THE COMPLEMENT SYSTEM IN NECROTIZING ANGIITIS OF THE SKIN. ANALYSIS OF COMPLEMENT COMPONENT ACTIVITIES IN SERUM OF PATIENTS WITH CONCOMITANT COLLAGEN-VASCULAR DISEASES*

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ABSTRACT

Profiles of serum complement components were studied in patients with necrotizing angiitis (vasculitis) of the skin and concomitant rheumatoid arthritis, Sjögren's syndrome, or systemic lupus erythematosus. In patients with either rheumatoid arthritis or Sjögren's syndrome, the early components—C1, C4, and C2—were depressed. When cryoglobulins containing mainly IgG and IgM were present in the patients with Sjögren's syndrome, there was further preferential reduction of C4 and C2 in serum and functionally active C1 molecules were present in the cryoprotein. A patient with Sjögren's syndrome and a cryoprotein containing large amounts of IgA exhibited depression of C3 levels with sparing of the early components, presumably reflecting activation of an alternate pathway of C3 consumption. Patients with systemic lupus erythematosus and vasculitis presented abnormalities of both early and late components of the complement system with a striking depression of C1q levels.

The general terms necrotizing angiitis and vasculitis are applied to clinical syndromes associated with segmental inflammation involving the entire wall of the blood vessels. The variability in size of the involved blood vessels, the distribution of the vascular lesions, the frequency of involvement of various organ systems, and the presence of serologic abnormalities have allowed division into clinically recognized syndromes [1–3]. One form of necrotizing angiitis known as hypersensitivity angiitis [2] involves venules and arterioles of multiple organ systems, including the skin. The palpable, erythematous cutaneous lesions do not blanch with external pressure and may be associated with a polymorphous array of other lesions. The presence of immunoglobulins IgG or IgM and C3 in vascular skin lesions has been noted by immunofluorescence studies [4, 5] and the syndrome associated with mixed-type cryoglobulins has been associated with a marked reduction in serum complement components of the classical pathway [6].

In this study, components of the complement system were measured in the serum of patients with rheumatoid arthritis, Sjögren's syndrome, or systemic lupus erythematosus—each of which exhibited an accompanying vasculitis involving the skin. Different profiles were observed depending upon the collagen-vascular disease accompanying the cutaneous vasculitis and the presence and nature of the cryoproteins. In addition, a quantitative functional assessment of the $C\overline{1}$ in the cryoprecipitate was achieved by the technique of $C\overline{1}$ transfer [7].

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MATERIALS AND METHODS

Thirteen patients, of whom 9 were hospitalized and 4 ambulatory, with a polymorphous array of skin lesions —macules, wheals, papules, nodules, infarcts, and ulcers—were studied. A consistent feature in all of the patients was the presence of raised, erythematous lesions of various sizes that did not blanch with the application of external pressure and that occurred in crops that persisted for several days. Seven patients had rheumatoid arthritis, 4 Sjögren's syndrome, and 2 systemic lupus erythematosus. The patients were studied initially, serially throughout the course of their illnesses, and for from 7 to 24 months during remission if it occurred. Cutaneous vasculitis was histologically documented in all patients. The control population included normal persons and in some instances individuals with the same clinical diagnoses without vasculitis. Multiple blood specimens from each patient were collected, clotted at room temperature for 1 hr, and centrifuged in the cold; the sera were stored immediately in aliquots at −70°C.

Four-mm skin trephine biopsy specimens were taken from a skin lesion and an adjacent clinically normal area after infiltrating the periphery of both sites with lidocaine. The tissue was fixed in 10% formalin, stained with hematoxylin-eosin, and examined with a light microscope.

The histopathologic criteria [8] used for the diagnosis of vasculitis of the small, superficial capillaries and venules of the skin (in biopsy specimens stained with hematoxylin-eosin) were: endothelial swelling, necrosis of the blood-vessel wall with the presence of fibrinoid material, an infiltrate composed predominantly of polymorphonuclear leukocytes in and about the blood-vessel walls and scattered in the dermis, fragmentation of nuclei

(nuclear dust), and extravasation of red-blood cells. All of the skin lesions, regardless of size, location, or clinical morphology, showed similar microscopic changes.

Laboratory studies obtained on each patient included: hematocrit, hemoglobin, erythrocyte sedimentation rate, white-blood cell count with differential analysis, eosinophil and platelet counts, antinuclear [9] and rheumatoid factors [10], serum electrophoresis, cold agglutinins, serologic test for syphilis, blood-chemistry profile (SMA-12), blood urea nitrogen, serum creatinine, urinalysis with sediment examination, creatinine clearance, 24-hr urine protein, electrocardiogram, and chest film.

Measurement of Complement Components

Veronal-buffered saline, pH 7.5, ionic strength 0.15 M, containing 0.1% gelatin, 0.00015 M Ca^{++}, 0.0005 M Mg^{++} (GVB^{++}) and dextrose–veronal-buffered saline, ionic strength 0.075 M ($DGVB^{++}$) [11], and 0.01 M or 0.04 M disodium ethylene diamine tetracetate (EDTA) [12] were prepared as previously described. Sheep erythrocytes were coated with rabbit antisheep hemolysin to obtain EA. $EAC1^{KP}$ cells were prepared in $DGVB^{++}$ by interacting EA at 1×10^8 cells/ml with an equal volume of $C\bar{1}^{KP}$ diluted to provide 200 effective molecules per cell in the fluid phase. After incubation for 90 min at 0°C, the cellular intermediate was washed once in $DGVB^{++}$ and stored in the same buffer with penicillin and streptomycin [13]. EAC1 cells were mixed with 2.5 times the EAC1 cell volume of pooled human serum diluted 1:10 in 0.01 M EDTA and incubated for 10 min at 0°C to yield EAC4 [14]; the EAC4 cells were washed and incubated twice at 37°C for 30 min in 0.04 M EDTA and resuspended in $DGVB^{++}$. EAC14 cells were prepared by incubating EAC4 cells at 5×10^8/ml with $C\bar{1}^{KP}$ to provide 200 effective molecules per cell in the fluid phase [15]; after incubation at 30°C for 10 min, the cellular intermediate was washed once in $DGVB^{++}$ and stored in the same buffer. EAC1–8 cells were prepared by interacting EAC14 at 5×10^8 cells/ml in $DGVB^{++}$ with an equal volume of a C2–8 reagent for 30 min at 30°C followed by washing in $DGVB^{++}$ and resuspension at 1×10^8 cells/ml in GVB^{++} before use [16]. Effective molecule titrations with these cellular intermediates were used to measure C1[17], C4[13], C2[15], C3[18], and C9[16]. Whole serum complement activity, CH_{50}, was measured as described [19]. C1q[20], C4[21], C3[20], C5[22], factor B[23], and $C\bar{1}$ inhibitor [24] were measured immunochemically by radial immunodiffusion [25].

Evaluation of Immunoglobulins and Cryoproteins

Serum immunoglobulins IgG, IgM, and IgA[26], IgD[27], and IgE[28] were measured by radial immunodiffusion. Screening for low molecular weight (7S) IgM was carried out in 4% polyacrylamide gel [29]. Fifty ml of blood were drawn into plastic syringes at 37°C and distributed for the isolation of cryoproteins into 2 glass tubes for 1 hr at 37°C to obtain serum and plasma formed in EDTA (1.4 mg/ml). The specimens were sedimented at 250 *g* for 10 min at 37°C. In order to determine the cryocrit, 1.0 ml portions of the serum and plasma were transferred to calibrated tubes (Clay, Adams, Becton & Dickinson Company) that were maintained at 4°C for 24 hr, followed by centrifugation at 250 *g* for 10 min.

In order to isolate the cryoproteins, 10 ml aliquots of the aforementioned serum and plasma were placed into glass tubes at 4°C for 24 hr and centrifuged at 5,000 *g* for 10 min at 4°C; the supernatant fraction was discarded. The precipitates were washed 3 times with $DGVB^{++}$ at the same temperature and redissolved in the same buffer at 37°C. The undissolved material was removed by centrifugation at 250 *g* for 10 min at 37°C. The cryoproteins were reprecipitated by incubation at 4°C for 1 hr, the precipitate was washed once in $DGVB^{++}$ and redissolved at 37°C in 1.0 ml GVB^{++}. The protein concentration of the redissolved cryoprecipitate was measured colorimetrically using the Folin–Ciocalteu phenol reagent [30]. The redissolved cryoprecipitates also were analyzed for their content of IgG, IgM, IgA, C1q, C4, and C3 by radial immunodiffusion at 37°C, and for their content of albumin and transferrin by Ouchterlony agar diffusion at 37°C [31].

The number of $C\bar{1}$ molecules bound to the cryoglobulin was determined by $C\bar{1}$ transfer [7]. One-half ml dilutions of cryoglobulin in GVB^{++} were incubated with 0.5 ml of EAC4 cells at 1×10^8/ml in the same buffer at 30°C for 15 min. One-half ml of $C2^{KP}$ containing 100 effective molecules per cell was added, followed by incubation at 30°C for 15 min. The reaction was developed for 60 min at 37°C after the addition of 0.5 ml of 0.04 M EDTA and 1.0 ml of guinea-pig serum diluted in 0.04 M EDTA.

RESULTS

Patients with Rheumatoid Arthritis and Vasculitis (Table I)

Erythematous papules that did not blanch with the application of external pressure had been present in all of the patients from 10 days to 4 yr at the initial examination. Subcutaneous nodules were present in 5 of the patients and ulcers of the skin in 3. All 7 of the patients, of whom 3 were women, were hospitalized owing to an exacerbation of their joint disease. Peripheral neuropathy was present only in patient AH. Therapeutic regimens were variable and included gold thiomalate, aspirin, prednisone, hydroxychloroquine, indomethacin, or phenyl butazone in various combinations. There was no apparent relation between any particular therapeutic agent and the onset of the vasculitis.

White-blood cell counts ranged from 3,100 to 8,000 and were low in patients JP and PD; eosinophilia, as assessed by total eosinophil counts, was present in patients WN and JP. Platelet counts were in the normal range, and cryoproteins were absent in all of the patients. Renal involvement was present in patients JC and EB as manifested by an abnormal urine sediment containing red-blood cells, an elevated blood urea nitrogen and serum creatinine, and a diminished creatinine clearance. Examination of a renal biopsy specimen obtained at another institution from patient EB showed glomerulitis. A postmortem examination of patient JC showed arteriolar nephrosclerosis of renal vessels; however, there was vasculitis involving the larger arterial vessels of the prostate, muscles, and heart that was accompanied by rheumatoid nodules of both pulmonic and mitral valves.

The titer of rheumatoid factor ranged from negative to 1:40,960 and the titer of antinuclear factor from negative to 1:5,120. Analysis of serum

TABLE I

Patients with rheumatoid arthritis and vasculitis

Patient	AH	AD	WN	JP	PD	JC	EB	
Age, sex	51 F	71 M	55 M	54 F	48 F	67 M	57 M	
Duration arthritis (yrs)	11	1	13	36	11	2	3	
Duration vasculitis	3 wks	10 days	2 wks	4 yrs	6 mos	2 mos	2 mos	
Ulcers	+	–	+	+	–	–	–	
Nodules	+	–	+	+	+	+	–	
								Normal* values
Rheumatoid factor	1:640	–	1:5120	1:40960	1:20480	1:20240	1:10240	
Antinuclear factor	trace	–	–	1:5120	1:320	trace	trace	
Immunoglobulins								
IgG (mg/ml)	9.05	10.0	[16.3]	10.3	14.05	9.75	12.6	7.2–15.8
IgM (mg/ml)	0.51	[0.44]	1.19	1.62	1.39	[2.53]	[2.3]	0.5–2.0
IgA (mg/ml)	2.79	2.36	5.31	3.06	1.58	3.43	1.2	1.0–5.6
IgD (μg/ml)	55.0	43.0	24.0	21.5	[9.2]	20.0	31.4	15–68
7S IgM	–	–	–	+	–	ND**	+	
Profiles of complement components at the initial examination								
Hemolytic assays (units/ml)								
CH_{50}	170.0	[253.0]	184.0	[88.0]	[113.0]	[113.0]	[118.0]	150–250
C1	226,000	237,000	264,000	[60,900]	224,200	237,000	[83,500]	141,300–287,900
C4	275,000	292,700	359,000	[114,000]	[95,120]	[73,900]	260,500	145,000–380,900
C2	17,200	[30,300]	18,020	[12,200]	[14,300]	[14,600]	[6,700]	15,500–27,400
C3	25,500	[48,500]	24,400	21,600	13,300	[4,000]	15,500	10,600–26,100
C9	[335,000]	[269,000]	[485,000]	[229,000]	[240,000]	[250,000]	[341,000]	136,900–219,600
Complement proteins								
C1q (μgN/ml)	26.0	37.0	28.0	30.0	26.5	37.4	24.0	18–38
C4 (μg/ml)	299.0	703.0	247.0	[118.0]	[100.0]	[132.0]	650.0	158–745
C3 (mg%)	108.0	169.0	110.0	97.0	122.0	[58.0]	125.0	91–198
C5 (μg/ml)	122.0	176.0	177.0	121.0	146.0	121.0	155.0	65–184
$C\bar{1}INH$ (mg %)	3.0	3.1	2.6	[4.8]	3.0	[5.0]	3.4	1.6–3.7
Factor B (%)	136.0	[230.0]	133.0	79.0	129.0	[61.0]	101.0	60–160

* Based on an analysis of 50 randomly selected healthy hospital personnel (normal values represent ± 2 SD).
** ND = not done; numbers within boxes are abnormal values.

immunoglobulins showed random changes in IgG, IgM, and IgD levels in some patients with normal levels of IgA and IgE. Low-molecular-weight (7S) IgM was present in serum of 2 of the patients.

In the 3 patients in whom the vascular skin lesions were present less than 4 weeks, (shown on the left side of Table I), the complement levels were normal or elevated both initially and at 2 or 3 subsequent analyses. In patient AD, in whom hypercomplementemia was present, particularly the levels of C3 and factor B were elevated. In the 4 patients in whom the vascular skin lesions were present more than 4 weeks, (shown on the right side of Table I), the CH_{50} levels were reduced. In these patients, the early components of the complement system—C1, C4, and C2—were low, although all the components were not necessarily depressed at the same time in each individual. C1, C4, and C2 were low in patient JP; C1 was normal in patients PD and JC with low levels of C4 and C2; and C1 and C2 were low in patient EB with normal levels of C4. The level of C1q remained in the normal range in patient JP and decreased in patient EB to 12.0 μg N/ml. C3 was in the normal range except in patient JC, in whom it was low; in addition, this was the only patient in whom factor B was at the lower limit of normal. C5, when assessed as a protein, was in the normal range and functional C9 was elevated in all 4 patients. The $C\bar{1}INH$ was elevated in patients JP and JC. In patients PD and JP there was complete resolution of cutaneous lesions with concomitant correction of

complement abnormalities to normal levels and a decrease in the titer of rheumatoid factor. Whole complement levels were in the normal range in 10 patients with rheumatoid arthritis without vasculitis, and did not show a range of variability as recorded in a series [32] comprising larger numbers of patients including some individuals with vasculitis.

Patient's with Sjögren's Syndrome and Vasculitis (Table II)

The skin lesions in these patients were clinically similar to those seen in individuals with rheumatoid arthritis and vasculitis and occurred as erythematous papules that did not blanch with the application of external pressure. The skin of the lower extremities was the predominant site of involvement, and the eruption appeared regularly after mild exercise. Erythematous lesions were observed on the palms and soles in patient HG. Ulcers of the skin were present in 2 patients, and hyperpigmentation of the skin of the lower extremities was present in 2 patients.

All of the patients were females and were hospitalized for evaluation. The sicca complex, parotid gland enlargement, and polyarthralgias that pre-

TABLE II

Patients with Sjögren's syndrome and vasculitis

	Patient			
	HG	RK	EK	MM
Age, sex	37 F	50 F	67 F	46 F
Duration vasculitis	17 yrs	8 yrs	6 mos	3 yrs
Ulcers	–	–	+	+
Hyperpigmentation	+	–	–	+
Sicca complex	+	+	+	+
Parotid enlargement	+	+	+	+
Arthralgias	+	+	+	+
Raynaud's phenomenon	+	+	–	+
Renal tubular acidosis	+	–	–	+
Rheumatoid factor	1:2560	1:1280	–	1:2560
Antinuclear antibody	1:160	1:20	1:20	1:10
Immunoglobulins				
IgG (mg/ml)	10.5	10.7	13.5	9.9
IgM (mg/ml)	0.8	1.75	1.92	0.6
IgA (mg/ml)	4.18	1.1	1.98	2.8
IgD (μg/ml)	29.5	[0]	[7.5]	[8.5]
7S IgM	–	+	+	+
Cryoglobulin	–	+	+	+
Profiles of complement components at the initial evaluation				
Hemolytic assays (units/ml)				
CH_{50}	190	[47]	[28]	[146]
C1	[340,800]	[87,800]	199,000	255,000
C4	324,800	[6,000]	[2,600]	300,000
C2	24,500	[4,100]	[6,700]	26,600
C3	20,500	14,900	16,600	[9,600]
C9	[226,500]	214,000	[257,500]	[134,000]
Complement proteins				
C1q (μgN/ml)	28	27	26	25
C4 (μg/ml)	486	[<40]	[47]	514
C3 (mg%)	125	125	158	[73]
C5 (μg/ml)	[243]	101	188	111
$C\bar{1}INH$ (mg%)	2.9	3.1	2.8	2.6
Factor B (%)	96	97	110	75

dominantly involved the ankles occurred in all of the patients. Raynaud's phenomenon was present in 3 of the 4 individuals. In patient EK, a lung biopsy specimen showed discrete and confluent collections of lymphocytes, plasma cells, histiocytes, and foreign-body granulomata in alveolar septa, as well as obliteration of the lung architecture; both septal and pleural fibrosis were present. These changes were interpreted as pseudolymphoma of the lung. A hypercellular bone marrow containing many megakaryocytes, myeloid, and erythroid hyperplasia, and a diffuse increase in reticulin fibers was considered to represent myelofibrosis.

At the initial evaluation, therapeutic regimens were variable and consisted of prednisone in patient HG, and hydroxychloroquine in patient MM, who formerly was treated with prednisone and penicillamine. Patients RK and EK were not receiving therapy.

White-blood cell counts and platelet counts were in the normal range in all patients; eosinophilia occurred in patient RK. Renal involvement was present in patients HG and MM in the form of renal tubular acidosis, as assessed by the inability to excrete an acid load after oral challenge with ammonium chloride [33]; urine-sediment examination, blood urea nitrogen, serum creatinine, 24-hr urine protein, and creatinine clearance were in the normal range.

The titer of rheumatoid factor ranged from negative to 1:2,560 and the antinuclear antibody titer from 1:10 to 1:160. Analysis of serum immunoglobulins showed normal levels of IgG, IgM, IgA, and IgE, with low levels of IgD in 3 patients. Low molecular weight (7S) IgM occurred in serum of 3 individuals, in whom cryoproteins in the form of cryoglobulins without cryofibrinogens also were present (Table III). The cryocrit in serum ranged from trace amounts to 21%. All of the cryoglobulins contained IgG, IgM, and IgA in varying ratios, as well as C1q; C4, C3, albumin, and transferrin were absent. Functionally active $C\bar{1}$ molecules were detectable in the cryoglobulins in amounts ranging from 7,100 to 17,000 units/ml.

TABLE III

Analysis of cryoglobulins

	Patient		
	RK	EK	MM
Cryocrit in serum (%)	<1	11	21
IgG (mg/ml)	<0.01	0.8	1.20
IgM (mg/ml)	0.015	0.45	0.002
IgA (mg/ml)	<0.01	<0.01	3.9
C1q (μgN/ml)	0.022	2.45	3.4
C4	—	—	—
C3	—	—	—
$C\bar{1}$ (units/ml)*	7,100	17,600	12,600
Albumin	—	—	—
Transferrin	—	—	—
Folin (O.D. 700 nm)	0.126	0.446	0.443

* The concentration of cryoproteins for $C\bar{1}$ transfer was 5-fold as compared to the serum from which it was obtained. The results of $C\bar{1}$ transfer are expressed as $C\bar{1}$ units/ml of starting serum.

Assessment of the complement system in serum showed low CH_{50} levels in the 3 patients with both cryoglobulins and 7S IgM, and a normal CH_{50} level in patient HG, in whom there was no cryoglobulin or 7S IgM. The levels of C1, C4, and C2 were low in patient RK, whereas in patient EK C4 and C2 were diminished with normal C1. In the patients with IgG–IgM cryoglobulins, it is of note that there were marked preferential reductions in C4 and C2. C1q and functional C1 levels remained normal in patient EK, whereas in patient RK the initial low level of functional C1 was followed by continued gradual decrease with reduction of C1q to 5.0 μg N/ml. Levels of C3, factor B, and C5 were normal, and there was a modest elevation of C9.

The cryoglobulin in patient MM contained predominantly IgA, and the complement profile in serum was characterized by slight reduction of C3 and C9. Factor B was in the normal range but was low when compared to levels in the other patients. During subsequent serial evaluations, the C3 fluctuated between normal and low levels.

In 3 patients with Sjögren's syndrome without vasculitis, the complement component profile as assessed by radial immunodiffusion was normal.

Patients with Systemic Lupus Erythematosus and Vasculitis (Table IV)

The onset of vascular lesions in these 2 hospitalized female patients was during an exacerbation of the systemic disease. The erythematous papules were associated with arthralgias, fever, peritonitis caused by *Diplococcus pneumoniae*, cytoid body of the left fundus, and urticaria resulting from light emitted over 290–320 nm and 360–600 nm in patient DF, and with arthralgias, fever, Raynaud's phenomenon, hypertension, anemia, and pleural effusion in patient SS; therapeutic regimens consisted of prednisone in both patients plus azathioprine in patient SS. In patient DF, the skin lesions cleared as the systemic disease improved; in patient SS the vasculitis was episodic in nature and occurred with some but not all exacerbations of the systemic process.

The white-blood cell count was 2,000 in patient DF and 6,300 in patient SS. Cryoproteins were absent and platelet counts were in the normal range. Renal involvement was present in patient DF as manifested by proteinuria and red-blood cells in the urine sediment, although the serum creatinine and creatinine clearance were in the normal range. Renal involvement was also present in patient SS as indicated by proteinuria, red-blood cells in the urine sediment, elevated levels of both blood urea nitrogen and serum creatinine and diminished creatinine clearance.

TABLE IV

Patients with systemic lupus erythematosus and vasculitis

	Patient	
	DF	SS
Age, sex	28 F	53 F
Duration vasculitis	1 day	12 yrs
Antinuclear factor	1:2560	1:640
Immunoglobulins		
IgG (mg/ml)	16.5	5.3
IgM (mg/ml)	1.27	0.13
IgA (mg/ml)	3.06	2.7
IgD (μg/ml)	13.0	12.0
Profiles of complement components at the initial evaluation		
Hemolytic assays (units/ml)		
CH_{50}	36	80
C1	17,500	34,600
C4	44,600	66,500
C2	6,000	4,200
C3	ND*	ND
C9	136,000	88,500
Complement proteins		
C1q (μgN/ml)	<1	<2
C4 (μg/ml)	90	124
C3 (mg%)	76	71
C5 (μg/ml)	211	155
$C\bar{1}INH$ (mg %)	4.8	3.4
Factor B (%)	54	62

* ND = not done.

The titer of antinuclear factor was 1:2,560 in patient DF and 1:640 in patient SS. Analysis of serum immunoglobulins in patient DF showed elevated levels of IgG with low levels of IgD and normal levels of IgM, IgA, and IgE; in patient SS there were low levels of IgG, IgM, and IgD with normal levels of IgA and IgE.

A low CH_{50} level was present in both patients, and the levels of C1, C4, and C2 were low with undetectable levels of C1q. The levels of C3, factor B, and C9 were low. In patient DF, the complement abnormalities returned to normal as the systemic disease improved during therapy, whereas the systemic disease remains active in patient SS, and the hypocomplementemia persists despite treatment.

DISCUSSION

Complement-component depletion in serum was recognized in 9 of 13 patients with cutaneous vasculitis associated with various collagen-vascular diseases. In spite of the polymorphous appearance of the clinical lesions in the skin of the 13 patients studied, purpuric papules were invariably present. Upon examination of tissue biopsy specimens, this form of vasculitis involved the superficial blood vessels. Although the site of involvement in these lesions was thought formerly to be arterioles [8], it is now clear that the damage occurs in the capillaries and venules which are the only vessels that reside in the most superficial portions of the dermis [34]. However, in more extensive disease, the blood vessels that are present in the deeper portions of the dermis and subcutaneous tissue may be involved.

In the patients with rheumatoid arthritis, the vascular lesions were not related to the duration of arthritis. Although it has been suggested that vasculitis occurs rarely if ever in patients with rheumatoid arthritis without rheumatoid factor [35], vasculitis did occur in 1 patient (AD) without rheumatoid factor. For the most part, however, the duration and evolution of the vasculitis seemed to correlate with the levels of rheumatoid factor and involvement of the complement system. When the vascular lesions were present less than 1 month, the rheumatoid factor tended to be low or absent, and the complement system was normal. When the skin lesions were present longer than 1 month, the rheumatoid factor titer was high, and the complement system was abnormal. Moreover, the titer of rheumatoid factor diminished in 2 patients (JP, PD), in whom the vascular lesions cleared and the complement levels returned to normal.

When the complement system in serum is involved in patients with rheumatoid arthritis and vasculitis, the early components—C1, C4, and C2—are preferentially reduced. Hypocomplementemia with a similar component profile was previously noted in a small percentage of patients with rheumatoid arthritis without a unifying clinical presentation [32, 36]. A similar utilization profile was observed in synovial fluid in patients without concomitant depression of complement components in serum [37]. The reduction in C3 levels in patient JC, in whom the levels of factor B were also low, suggests the importance of recruitment of an amplification mechanism [23]. Although postmortem examination in this patient showed vasculitis involving some internal organs, the kidneys showed arteriolar nephrosclerosis without vasculitis, suggesting that the complement abnormalities were not related to the renal disease. The presence of 7S IgM noted previously in patients with rheumatoid arthritis [38] was not associated with clinical features, distinguishing patients JP and EB from the rest of the patients.

Previously recognized cutaneous manifestations in Sjögren's syndrome [39, 40] were related to the sicca complex with dry mucosae and skin or to the associated collagen-vascular disease, such as systemic lupus erythematosus. The nature of the purpura in patients with Sjögren's syndrome in whom skin biopsy examinations are reported is a

vasculitis [41]. In our patients, the skin lesions were documented as vasculitis by histopathologic studies.

Hypocomplementemia was present in 3 of 4 patients with Sjögren's syndrome, in whom both cryoglobulins and 7S IgM were present. In the 2 individuals with the cryoglobulin containing predominantly IgG and IgM, the levels of C4 and C2 were strikingly diminished, consistent with activation of C1. The fixation of C1 is reflected both by reduction of the level in serum in patient RK and by its presence in isolated precipitates as measured both antigenically and functionally by $C\overline{1}$ transfer. In the patient with a cryoglobulin composed of IgG and IgA, the level of C3 in serum was low in the presence of normal levels of C1, C4, and C2. Inasmuch as it was shown in vitro [42] that aggregated IgA activates the complement system independent of classical or early components, the profile in this patient may represent an example in vivo of this phenomenon.

In patients with systemic lupus erythematosus, the low incidence of hypersensitivity angiitis of the skin is of note [43]. A striking feature of the 2 patients with vasculitis is the low level of C1q. Low levels of C1q were reported in patients with systemic lupus erythematosus [44], deposits of C1q were detected in the glomerulus of patients with nephritis in systemic lupus erythematosus [45], and a study of the metabolism of C1q molecule in 1 patient with systemic lupus erythematosus showed increased utilization [46]. However, in the latter study, the patient possessed a cryoprotein that took up the labeled C1q. In addition to the finding of low C4 and C2 indicating activation of the classical pathway, these patients showed reduced levels of factor B and C9, consistent with involvement of an amplification mechanism which intensifies the utilization of terminal components, as has been observed previously in systemic lupus erythematosus associated with nephritis [23].

Although the clinical manifestations and histopathologic changes of necrotizing angiitis of the skin were comparable within the 3 patient groups, the complement-component profiles appear to be distinctly different. Indeed, the complement profiles are consistent with existing data in patients with these particular collagen-vascular diseases. Thus, in patients with rheumatoid arthritis there was evidence for activation of C1 with utilization of C4 and C2; in patients with Sjögren's syndrome, the depletion of C4 and C2 was even more marked when cryoglobulin containing IgG and IgM was present; in a single patient with Sjögren's syndrome in whom the cryoglobulin contained IgG and IgA, the complement abnormalities were consistent with activation of the alternate complement sequence independent of involvement of the classical or early components; and in patients with systemic lupus erythematosus, the profound depletion of C1q and apparent recruitment of an amplification mechanism with utilization of the terminal sequence is entirely reminiscent of findings in patients with systemic lupus erythematosus with active renal disease.

It is not possible to determine whether the abnormalities of the complement profile are a cause or a consequence of the necrotizing angiitis of the skin or whether they are merely a concomitant event related to the underlying disease process. Nevertheless, in the differential diagnosis of patients with cutaneous necrotizing angiitis, the complement component profile in serum may be of predictive value in allowing anticipation of an underlying collagen-vascular disease or the presence of a cryoprotein.

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